National Institute for Health and Clinical Excellence

Single Technology Appraisal (STA)

Bendamustine for the treatment of chronic lymphocytic leukaemia

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Comment 1: the draft remit

Section	Consultees	Comments	Action
Appropriateness	Leukaemia Research	Yes	Comment noted. It was agreed at the scoping workshop that an appraisal of bendamustine for CLL was appropriate.
	Royal College of Pathologists and BSH	Yes, it would be appropriate for NICE to appraise bendamustine in CLL	Comment noted. It was agreed at the scoping workshop that an appraisal of bendamustine for CLL was appropriate.
	Sheffield PCT/North Trent Cancer Network	Yes	Comment noted. It was agreed at the scoping workshop that an appraisal of bendamustine for CLL was appropriate.
	Napp Pharmaceuticals	It is appropriate to refer this topic to NICE as the technology offers significant advantages to standard therapy in patients not suitable for fludarabine based regimens in the first line setting.	Comment noted. It was agreed at the scoping workshop that an appraisal of bendamustine for CLL was appropriate.
	Royal College of Physicians	Yes. There are various new agents coming along for the treatment of newly diagnosed and relapsed patients with CLL. Bendamustine has been around a long time principally available in the old East Germany but it has now got a fully complete phase III trial supporting its use especially as it appear to show superiority to chlorambucil, therapy.	Comment noted. It was agreed at the scoping workshop that an appraisal of bendamustine for CLL was appropriate.

Section	Consultees	Comments	Action
	Royal College of Nursing	This seems appropriate	Comment noted. It was agreed at the scoping workshop that an appraisal of bendamustine for CLL was appropriate.
	Lymphoma Association	Yes, it would be appropriate for NICE to appraise bendamustine in CLL	Comment noted. It was agreed at the scoping workshop that an appraisal of bendamustine for CLL was appropriate.
Wording	Leukaemia Research	Yes - but it appears to be based on an assumption of eventual licensing for this indication	To provide timely guidance to the NHS the remits and scopes for an appraisal are developed before marketing authorisation. Guidance can only be issued in accordance with the marketing authorisation.
	Royal College of Pathologists and BSH	Yes, although bendamustine does not yet have UK marketing authorisation for this indication.	To provide timely guidance to the NHS the remits and scopes for an appraisal are developed before marketing authorisation. Guidance can only be issued in accordance with the marketing authorisation.
	Sheffield PCT/North Trent Cancer Network	Yes	Comment noted. No actions required.
	Napp Pharmaceuticals	Yes	Comment noted. No actions required.
	Royal College of Physicians	Yes	Comment noted. No actions required.

Section	Consultees	Comments	Action
	Lymphoma Association	Yes, although the remit does not point out until page 2 that at the moment bendamustine does not yet have UK marketing authorisation. For the purposes of clarity it might be best to stress at the outset that this discussion is taking place in anticipation of marketing authorisation.	To provide timely guidance to the NHS the remits and scopes for an appraisal are developed before marketing authorisation. Guidance can only be issued in accordance with the marketing authorisation.
	Chronic Lymphocytic Leukaemia Support Association (CLLSA)	Since the natural history of CLL is so long, consider using minimal residual disease where (if) the data is available.	Comment noted. It was agreed at the scoping workshop that the outcomes for the appraisal were appropriate.
Timing Issues	Leukaemia Research	Timing is appropriate	Comment noted. No actions required.
	Royal College of Pathologists and BSH	It is timely (assuming marketing authorisation is not delayed unduly). However, it is likely that the main comparator (chlorambucil monotherapy) will be replaced by chlorambucil plus an anti-CD20 antibody (either rituximab or ofatumumab) within the next few years as the standard of care for less fit patients (see below).	Comment noted. It was agreed at the scoping workshop that chlorambucil was the appropriate comparator.
	Sheffield PCT/North Trent Cancer Network	Original covering letter not seen. As there are alternative effective treatments available, this is not high priority	Comment noted. It was agreed at the scoping workshop that an appraisal of bendamustine for CLL was appropriate.
	Napp Pharmaceuticals	The suggested timing is appropriate	Comment noted. No actions required.

Section	Consultees	Comments	Action
	Royal College of Physicians	High - if one is deemed unsultable for fludarabine/cyclophosphamide +/- rituximab then there are virtually no other suitable therapies other than chlorambucil. Bendamustine looks as if it may add to the list of agent available for patients unsuitable for FCR therapy. However, there has been no formal comparison of FCR with Bendamustine and hence one could/should argue that one should only be appraising whether bendamustine is a suitable option for patients not suitable for FCR or for that matter any fludarabine based regimen.	Comment noted. It was agreed at the scoping workshop that chlorambucil was the appropriate comparator and that the appropriate population was people for whom fludarabine chemotherapies were not appropriate.
	Lymphoma Association	An STA for bendamustine would be timely assuming that marketing authorisation is not delayed. Future alternatives to current standard comparators will need to be taken into consideration in future reviews of guidance on bendamustine.	Comment noted. No actions required.
Additional comments on the draft remit		None received	

Comment 2: the draft scope

Section	Consultees	Comments	Action
Background information	Leukaemia Research	Yes	Comment noted. No actions required.
	Royal College of Pathologists and BSH	The background information is reasonable, although it should perhaps emphasise that patients with CLL who need treating have an impaired quality of life owing to symptoms of tiredness and general malaise, and that effective treatment makes CLL patients feel better and restores good quality of life. Indeed, this is one for the key aims of treatment. It should also explain that CLL runs a chronic relapsing course, and that most patients therefore require more than one treatment episode during the course of their disease.	Comment noted. The background section of the scope refers to improvement in quality of life and has been amended to refer to chronic relapsing course with people requiring more than one treatment episode during the course of their disease.
	Sheffield PCT/North Trent Cancer Network	The fact that the majority of patients will not require treatment for their CLL should be included	Comment noted. The scope refers to the role of 'watchful waiting' in people with early stage disease or with non-symptomatic disease.
	Napp Pharmaceuticals	The information is accurate. However it is important to note that 30-50% of patients in the UK are fit enough to tolerate an efficacious course of fludarabine in combination with cyclophosphamide and rituximab, as recommended by NICE (expert opinion). For those patients not eligible for fludarabine based treatment, the standard of care is currently chlorambucil.	Comment noted. The scope has been amended to refer to the use of chlorambucil in people who are not appropriate for fludarabine chemotherapies.
	Royal College of Physicians	Adequate	Comment noted. No actions required.

Section	Consultees	Comments	Action
	Lymphoma Association	It may be valuable to include reference to the symptoms of CLL in order to allow the appraisal committee to appreciate the significance of effective therapy for patients. Because CLL causes anaemia and fatigue, patients with the disease suffer from malaise and lack of energy that has a significant impairment on quality of life. Other symptoms include enlarged lymph nodes, enlarged liver and spleen, fatigue, bone pain, abnormal bruising, excessive sweating, loss of appetite, weight loss and re-occurring infections. It might also be worth referring to the staging of CLL, as patients with stage C disease may be a particular target audience for the technology in question. The Binet staging system defines Stage A as little solid disease and no bone marrow failure, Stage B as lots of solid disease but no bone marrow failure, and stage C as bone marrow failure.	Comment noted. This level of detail is not required in the scope document. This is important information to be included in the evidence submissions and statements that are presented to the Appraisal Committee. Consultees at the scoping workshop agreed that, if evidence allows, performance status, stage of disease and co-morbidities were all appropriate subgroups to include in the scope
	Chronic Lymphocytic Leukaemia Support Association (CLLSA)	The background information should include the fact that the selection of FCR or Chlorambucil, the current first line treatments, depend on the relative fitness of the patient. FCR is generally used when patients have few co-morbidities.	The background section has been amended to state that treatment options vary depending on factors such as stage of CLL, performance status, co-morbidities and genetic markers.
The technology/	Leukaemia Research	Yes	Comment noted. No actions required.

Section	Consultees	Comments	Action
Intervention	Royal College of Pathologists and BSH	The description of how bendamustine actually works is rather vague. On the other hand, its exact mechanism of action is not entirely clear. It is relevant to point out that the drug is administered via the intravenous route over two consecutive days for each cycle of treatment.	Comment noted. The technology section of the scope refers to administration by intravenous infusion. The cycle of treatment is not included in the scope document.
	Sheffield PCT/North Trent Cancer Network	Yes	Comment noted. No actions required.
	Napp Pharmaceuticals	The description is accurate but incomplete. Although bendamustine appears to be bi-functional on the basis of its structure, the situation is more complex. It does however have a unique mechanism of action which differentiates it from other alkylators. We suggest the following description which is taken from the current SmPC being approved through the decentralised procedure: "Bendamustine hydrochloride is an alkylating antitumour agent with unique activity. The antineoplastic and cytocidal effect of bendamustine hydrochloride is based essentially on a cross-linking of DNA single and double strands by alkylation. As a result, DNA matrix functions and DNA synthesis and repair are impaired. Bendamustine hydrochloride showed an activity profile in human tumour cell lines different to that of other alkylating agents. The active substance revealed no or very low cross-resistance in human tumour cell lines with different resistance mechanisms at least in part due to a comparatively persistent DNA interaction. Additionally, it was shown in clinical studies that there is no complete cross-resistance of bendamustine with anthracyclines, alkylating agents or rituximab. However, the number of assessed patients is small."	Comment noted. The technology section of the scope has been amended.The description of the technology in a scope does not include information on the activity of a technology nor clinical study results.

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	Royal College of Physicians	Not completely as there have been several studies assessing the potential role of bendamustine in both untreated and previously treated patients. There has been only 1 phase III randomised trial in CLL.	Comment noted. The technology section of the scope has been amended.
	Lymphoma Association	You could add that Bendamustine is administered intravenously over 2 days every 3 weeks for a total of 6 - 8 cycles.	Comment noted. The technology section of the scope refers to administration by intravenous infusion. The cycle of treatment is not included in the scope document.
	Chronic Lymphocytic Leukaemia Support Association (CLLSA)	Yes	Comment noted. No actions required.
Population	Leukaemia Research	Yes	Comment noted. No actions required.

Section	Consultees	Comments	Action
	Royal College of Pathologists and BSH	It is important to consider the effects of bendamustine in patients with stage C disease. These patients have impaired bone marrow function and are likely to be both harder to treat and more prone to haematological toxicity. Another group of patients who are worthy of special consideration are those with a deletion of p53 on the short arm of chromosome 17 (17p-). These patients have a short survival and tend to be resistant to chemotherapy. It is important to understand the potential value of bendamustine in this group of patients as many authorities believe that chemotherapy-based treatment should be avoided in favour of alemtuzumab-based regimens.	Comment noted. At the scoping workshop it was agreed that performance status, stage of disease and co-morbidities were all appropriate subgroups to be included in the scope; however people with p53 deletions would not be an appropriate subgroup of people to include as these people are not normally considered appropriate for chemotherapy regimens.
	Sheffield PCT/North Trent Cancer Network	Younger, fitter patients are preferentially treated with rituximab+FC. Older, less fit patients (who would not tolerate the above) is a sub group who may benefit more from this treatment. (For the very small number of patients with p53 deletions Campath would remain the preferred treatment)	Comment noted. At the scoping workshop it was agreed that performance status would be included as a subgroup of people in the scope.
	Napp Pharmaceuticals	No - the population should reflect the licensed indication which excludes patients suitable for fludarabine based chemotherapy. The correct population is: Previously untreated patients with chronic lymphocytic leukaemia (Binet stage B or C) for whom fludarabine combination chemotherapy is not appropriate.	Comment noted. The population has been amended in line with the proposed indication.

Section	Consultees	Comments	Action
	Royal College of Physicians	There is no evidence at present to our knowledge that Bendamustine preferentially targets a given subgroup of patients.	Comment noted. At the scoping workshop it was agreed that performance status, stage of disease and co-morbidities were all appropriate subgroups to be included in the scope.
	Lymphoma Association	Bendamustine may have a particular application for people with stage C disease, (see above) or people with disease characterised by a deletion of the p53 anti-tumour gene.	Comment noted. At the scoping workshop it was agreed that performance status, stage of disease and co-morbidities were all appropriate subgroups to be included in the scope; however people with p53 deletions would not be an appropriate subgroup of people to include as these people are not normally considered appropriate for chemotherapy regimens.
	Chronic Lymphocytic Leukaemia Support Association (CLLSA)	Yes, but see the comment on background information.	Comment noted. No actions required.
Comparators	Leukaemia Research	Yes	Comment noted. No actions required.

Section	Consultees	Comments	Action
	Royal College of Pathologists and BSH	It is appropriate to compare bendamustine with chlorambucil (Chl) as this is the current standard of care for less fit patients. However, Chl on its own may not remain the standard of care for less fit patients for very much longer. Thus NICE are planning to revisit Chl as a chemotherapy partner for rituximab once data from the Roche phase II trial are available. In addition, an ongoing NIHR phase III RCT is currently looking at a second-generation anti-CD20 antibody (ofatumumab) as an antibody partner to Chl. If, as is very likely to be the case, the combination regimen is shown to be superior to Chl alone, "O-Chl" will become the new standard of care for less fit patients. It is also clinically relevant to compare bendamustine with fludarabine in combination with cycophosphamide and rituximab (R-FC) which is the new standard of care for fit patients. However, no phase III randomised trials have made this comparison so it is difficult to know on what basis it will be made. A phase III RCT comparing R-FC with R-bendamustine is being developed by the German CLL study group, while another study is comparing R-Chl with R-bendamustine. These studies are likely to clarify the role of bendamustine-anti-CD20 antibody combinations in the context of modern treatments for both fit and less fit patients but will take several years before they yield any data.	Comment noted. The technology will be appraised in accordance with its licensed indication which the manufacturer has indicated is people who are not appropriate for fludarabine chemotherapies. It was agreed at the scoping workshop that the appropriate comparator was chlorambucil.
	Sheffield PCT/North Trent Cancer Network	See "population" above. Chlorambucil is the comparator for the older, less fit sub group.	Comment noted. The scope has been amended with chlorambucil being the single comparator in the scope.
	Napp Pharmaceuticals	No - fludarabine based regimens should be excluded in line with the marketing authorisation. We agree that the standard first line therapy in patients not suitable for fludarabine in the UK is chlorambucil	Comment noted. The scope has been amended with chlorambucil being the single comparator in the scope.

Section	Consultees	Comments	Action
	Royal College of Physicians	Yes. Basically FCR should be the standard treatment for all patients given the recent report showing superior overall survival compared to FC (and by inference chlorambucil which has been shown to be inferior to FC). However many patients are either deemed too unfit for FCR in which case Clb is the present standard treatment, or having received FCR are unable to tolerate at least 4 doses. Also around 5-10% of patients react with rituximab and hence FCR proves to be impossible to give.	Comment noted. The technology will be appraised in accordance with its licensed indication which the manufacturer has indicated is people who are not appropriate for fludarabine chemotherapies. It was agreed at the scoping workshop that the appropriate comparator was chlorambucil.
	Lymphoma Association	Chlorambucil is a suitable comparator but this may be superceded as the treatment of choice for frail patients pending results of trials currently in progress looking at antibody + chlorambucil. These trials are testing the addition of rituximab to chlorambucil, and the addition of ofatumumbab to chlorambucil. Trials are also comparing R-FC and R-Chl with R-Bendamustine however the results will not be forthcoming for some time	Comment noted. It was agreed at the scoping workshop that the appropriate comparator was chlorambucil.
	Chronic Lymphocytic Leukaemia Support Association (CLLSA)	Yes . The comparator is dependant on the patient's overall fitness. If FCR is used, then this combination has been shown to extend life expectancy for CLL patients. Please note that there is an ongoing trail of rituximab/chlroambucil for the less fit patient where data is building up.	Comment noted. It was agreed at the scoping workshop that the appropriate comparator was chlorambucil.
Outcomes	Leukaemia Research	Yes	Comment noted. No actions required.

Section	Consultees	Comments	Action
	Royal College of Pathologists and BSH	The outcome measures proposed are appropriate for CLL. Emphasis should be placed on the difficulty of showing survival benefit in a randomised trial in a chronic relapsing disorder such as CLL. The difficulty lies in the fact that many patients allocated not to receive the experimental treatment initially will go on to do so subsequently when they relapse. For this reason the international CLL community have recommend progression-free survival (PFS) as the most meaningful trial endpoint when assessing theeffectiveness of a new treatment. This idea is embodied in the recently published IWCLL guidelines.	Comment noted. No actions required.
	Sheffield PCT/North Trent Cancer Network	Yes	Comment noted. No actions required.
	Napp Pharmaceuticals	We suggest duration of response should also be considered	Consultees were in agreement at the scoping workshop that the outcomes listed in the draft scope were appropriate. Duration of response was not considered to be needed as a specific outcome in the scope.
	Royal College of Physicians	Yes	Comment noted. No actions required.
	Lymphoma Association	As it is difficult to demonstrate overall survival, emphasis should be placed on progression free survival and quality of life outcomes. Toxicity of therapy is also an important outcome measure, as this treatment is well tolerated and compares favourably to other therapies especially for those patients who are frail and those with renal impairment.	Comment noted. No actions required.

Section	Consultees	Comments	Action
	Chronic Lymphocytic Leukaemia Support Association (CLLSA)	PFS is a good measure of health related benefit. The number and degree of adverse events from the data would be a measure of harm.	Comment noted. No actions required.
Economic analysis	Royal College of Pathologists and BSH	The RCT on which this NICE appraisal will be largely based should be sufficiently mature to provide meaningful health economic analysis.	Comment noted. No actions required.
	Royal College of Physicians	Yes	Comment noted. No actions required.
	Chronic Lymphocytic Leukaemia Support Association (CLLSA)	Comparisons should be made at standard dosage levels.	Comment noted. No actions required.
Equality and Diversity	Royal College of Pathologists and BSH	There are no reasons to suspect that there are any equality issues to consider in this context of this appraisal.	Comment noted. No actions required.
	Royal College of Pysicians	As far as we can see - not relevant to the use of this particular agent.	Comment noted. No actions required.
	Lymphoma Association	Given perceived inequities in cancer treatment for older people, it is perhaps worth stressing that this disease is largely one of old age, and that effective management in old age necessitates a greater number of therapeutic alternatives.	Comment noted. It was agreed at the scoping workshop that there were no specific equalities issues that needed to be raised in the scope document.

Section	Consultees	Comments	Action
Other considerations	Royal College of Pathologists and BSH	Currently, many authorities believe that there should be three approaches to the first-line treatment of CLL depending on fitness and the presence of a p53 deletion. Although it has never been proved in a randomised trial (and is unlikely ever to be), patients with 17p- (5-10% of cases) are thought to benefit from alemtuzumab-based therapy in preference to a chemotherapy-based approach. For the majority of patients who do not have a p53 defect, R-FC is now considered the treatment of choice for fit patients, while chlorambucil (Chl) still remains the standard of care for less fit patients who are unable to tolerate R-FC. It is not entirely clear where bendamustine might fit into this framework. Thus, although it might appear to be more effective than Chl, it is also more toxic (grade 3-4 toxicity 40% versus 19% in the phase III RCT comparing it with Chl), and it is therefore unclear how well it would be tolerated by less fit patients who are unable to tolerate R-FC. There are also questions to ask about the efficacy of bendamustine since the median PFS in the phase III RCT comparing it with Chl was not particularly impressive (21.6 months) - strikingly similar to the the median PFS observed in the Chl arm of the UK CLL4 trial (20 months) and considerably shorter than the median PFS in the FC arm of the UK CLL4 trial (43 months). Importantly, the Chl regimen employed in the bendamustine trial was somewhat unconventional (at least for UK practice) and involved administering a relatively big dose on day 1 and 15 of each cycle rather than a more modest dose over 7 consecutive days as in the UK CLL4 trial. In other words, the apparent superiority of bendamustine over Chl might actually reflect the inadequacy of the Chl arm which produced median PFS of only 8.3 months. Alternatively, it could be that patients recruited into the UK CLL4 trial had a better risk profile. These are important questions that need to be addressed. One virtue of bendamustine is that, unlike fludarabine-base combinations, it can be used without dose attenuation in patients with renal impairment. The drug may therefore have a niche in this setting as a potentially more effective alternative to chlorambucil.	Comment noted. The technology will be appraised in accordance with its licensed indication which the manufacturer has indicated is people who are not appropriate for fludarabine chemotherapies. It was agreed at the scoping workshop that the appropriate comparator was chlorambucil.

Section	Consultees	Comments	Action
	Napp Pharmaceuticals Ltd	It is important to note that, for patients not suitable for fludarabine the standard of care is chlorambucil. Bendamustine has been shown to offer superior efficacy in terms of response and progression free survival over chlorambucil, and therefore offers another treatment option for these patients.	Comment noted. It was agreed at the scoping workshop that the appropriate comparator was chlorambucil.
Questions for consultation			
Additional comments on the draft scope.	Royal College of Nursing	The draft remit and draft scope seem appropriate. There are no further comments to make on it at this stage	Comment noted. No actions required.
	Chronic Lymphocytic Leukaemia Support Association (CLLSA)	I remain concerned that I cannot find a study where bendamustine is directly compared with other chemotherapy where the other chemotherapy is at standard dose levels, but I will keep looking.	Comment noted. No actions required.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Department of Health
GlaxoSmithKline
Leukaemia CARE
Macmillan Cancer Support
Marie Curie Cancer Care
National Public Health Service for Wales (now Public Health Wales NHS Trust)
NHS Quality Improvement Scotland
Rarer Cancers Forum
RICE - Research Institute for Care of Older People
Welsh Assembly Government